

**WHAT IS CLAIMED IS:**

1           1.       A method of extracting structural information from a NMR data set for  
2 a selected macromolecule in an intact biological compartment wherein said selected  
3 macromolecule is labeled with an NMR-detectable nucleus, such that said nucleus is present  
4 in said macromolecule in an amount greater than is naturally abundant in said  
5 macromolecule, said method comprising:

- 6           (a) contacting said cell with radio frequency energy, thereby producing an excited  
7                NMR-detectable nucleus;  
8           (b) collecting radio frequency data from said excited NMR-detectable nucleus,  
9                thereby producing said NMR data set, and  
10          (c) analyzing said data set to extract said structural information for said selected  
11                macromolecule from said data set.

1           2.       The method according to claim 1, wherein said selected  
2 macromolecule is overexpressed in said biological compartment.

1           3.       The method according to claim 1, wherein said NMR-detectable  
2 nucleus is present in an amount detectable by NMR of said biological compartment.

1           4.       The method according to claim 1, wherein said selected  
2 macromolecule is a member selected from the group consisting of proteins, saccharides,  
3 glycoproteins, and nucleic acids.

1           5.       The method according to claim 1, wherein said selected  
2 macromolecule is in a complex with a small molecule.

1           6.       The method according to claim 5, wherein said small molecule is an  
2 exogenous small molecule.

1           7.       The method according to claim 5, wherein said small molecule is a  
2 therapeutic agent or a candidate therapeutic agent.

1           8.       The method according to claim 7, wherein said small molecule is an  
2 exogenous small molecule.



9 (c) inducing said transformed biological compartment, thereby preparing said labeled  
10 biological compartment.

1 18. The method according to claim 17, further comprising:  
2 (d) inhibiting essentially all transcription in said transformed biological compartment,  
3 which is under control of promoters native to said unlabeled precursor  
4 biological compartment, while allowing transcription under control of said  
5 non-native promoter to proceed.

1 19. The method according to claim 17, wherein said medium comprises an  
2 amino acid labeled with said NMR sensitive nucleus.

1 20. The method according to claim 17, wherein said medium is deuterated.

1 21. The method according to claim 17, wherein said biological  
2 compartment is a bacterial cell.

1 22. The method according to claim 17, wherein the non-native promoter  
2 encodes an RNA polymerase that is operable during step (d).

1 23. The method according to claim 17, wherein the non-native promoter is  
2 a phage promoter.

1 24. The method according to claim 18, wherein said inhibiting is caused by  
2 administering an inhibitor to said biological compartment in an amount sufficient to cause  
3 said inhibiting.

1 25. The method according to claim 24, wherein said inhibitor is rifampicin.

1 26. The method of claim 1, wherein said selected macromolecule  
2 experiences a local viscosity at least 2 fold greater than the viscosity of pure water, wherein  
3 said local viscosity and said viscosity of said pure water are determined at the same  
4 temperature.

1 27. The method of claim 1, wherein said selected macromolecule is  
2 present in said biological compartment at a weight percent of up to 0.3% compared to the  
3 total weight of said biological compartment.

1                   28.     The method of claim 1, wherein said selected macromolecule is  
2 present in said biological compartment at a weight percent of up to 50% compared to the total  
3 weight of said biological compartment.

1                   29.     The method of claim 1, wherein said selected macromolecule has a  
2 molecular weight of at least 5 kDa.

1                   30.     The method of claim 1, wherein said selected macromolecule has a  
2 molecular weight of at least 25 kDa.

1                   31.     The method of claim 1, wherein said selected macromolecule has a  
2 molecular weight of at least 70 kDa.

1                   32.     The method of claim 1, wherein said biological compartment is a  
2 living cell.

1                   33.     The method of claim 1, wherein said biological compartment is a cell  
2 that has been metabolically arrested.

1                   34.     The method of claim 1, wherein said selected macromolecule is  
2 expressed from a plasmid.

1                   35.     The method of claim 1, using a multidimensional multinuclear method.

1                   36.     The method of claim 35, using an HNCA experiment.

1                   37.     The method of claim 35, using an HMQC experiment.

1                   38.     The method of claim 1, wherein said compartment is a biological cell.

1                   39.     The method of claim 38, wherein said cell is a prokaryotic cell.

1                   40.     The method of claim 39, wherein said cell is a *E. coli* cell.

1                   41.     The method of claim 38, wherein said cell is a eukaryotic cell.

1                   42.     The method of claim 41, wherein said cell is a yeast cell.

1                   43.     The method of claim 41, wherein said cell is a mammalian cell.

1           **44.**    The method of claim **43**, wherein said cell is a human cell.

1           **45.**    A method of extracting structural information from a NMR data set for  
2 a selected macromolecule of an intact biological compartment wherein said selected  
3 macromolecule is labeled with a NMR-detectable nucleus, such that said nucleus is present in  
4 said macromolecule in an amount greater than is naturally abundant in said macromolecule,  
5 wherein said nucleus is not  $^{19}\text{F}$ , said method comprising:

- 6           (a) contacting said biological compartment with radio frequency energy,  
7           thereby producing an excited NMR-detectable nucleus, and  
8           (b) collecting radio frequency data from said excited NMR-detectable  
9           nucleus, thereby producing said NMR data set.

1           **46.**    The method according to claim **45**, wherein said selected  
2 macromolecule is overexpressed in said biological compartment.

1           **47.**    The method according to claim **45**, wherein said NMR-detectable  
2 nucleus is present in an amount detectable by NMR of said intact, biological compartment.

1           **48.**    The method according to claim **45**, wherein said selected  
2 macromolecule is a member selected from the group consisting of proteins, saccharides,  
3 glycoproteins, and nucleic acids.

1           **49.**    The method according to claim **45**, wherein said selected  
2 macromolecule is in a complex with a small molecule.

1           **50.**    The method according to claim **49**, wherein said small molecule is an  
2 exogenous small molecule.

1           **51.**    The method according to claim **49**, wherein said small molecule is a  
2 therapeutic agent or a candidate therapeutic agent.

1           **52.**    The method according to claim **51**, wherein said small molecule is an  
2 exogenous small molecule.

1           **53.**    The method according to claim **45**, wherein said macromolecule is  
2 further labeled with deuterium.

1           **54.**     The method according to claim **45**, wherein said biological  
2 compartment is present in a suspension.

1           **55.**     The method according to claim **45**, wherein said structural information  
2 is conformational information.

1           **56.**     The method according to claim **45**, wherein said structural information  
2 is for a complex formed between said selected macromolecule and a small molecule selected  
3 from therapeutic agents and candidate therapeutic agents.

1           **57.**     The method according to claim **45**, wherein said structural information  
2 is for a complex formed between said selected macromolecule and a member selected from  
3 small molecules, endogenous macromolecules and combinations thereof.

1           **58.**     The method according to claim **45**, wherein said structural information  
2 is for a first conformation of said selected macromolecule and a second conformation of said  
3 selected macromolecule.

1           **59.**     The method according to claim **45**, wherein said data set is acquired by  
2 a triple resonance NMR method.

1           **60.**     The method according to claim **59**, wherein said triple resonance NMR  
2 experiment is a member selected from HSQC and TROSY.

1           **61.**     The method according to claim **45**, wherein said biological  
2 compartment is prepared by a method comprising:

- 3           (a) transforming an unlabeled precursor of said labeled biological compartment with  
4               a nucleic acid encoding said selected macromolecule, wherein said nucleic  
5               acid is operably linked to a promoter non-native to said unlabeled precursor  
6               biological compartment, thereby producing a transformed biological  
7               compartment;  
8           (b) incubating said transformed biological compartment in a medium comprising said  
9               NMR-detectable nucleus; and  
10          (c) inducing said transformed biological compartment, thereby preparing said labeled  
11               biological compartment.

1           **62.**     The method according to claim **61**, further comprising:  
2           (d) inhibiting essentially all transcription in said transformed biological compartment,  
3           which is under control of promoters native to said unlabeled precursor  
4           biological compartment, while allowing transcription under control of said  
5           non-native promoter to proceed.

1           **63.**     The method according to claim **61**, wherein said medium comprises an  
2           amino acid labeled with said NMR sensitive nucleus.

1           **64.**     The method according to claim **61**, wherein said medium is deuterated.

1           **65.**     The method according to claim **61**, wherein said biological  
2           compartment is a bacterial cell.

1           **66.**     The method according to claim **61**, wherein the non-native promoter  
2           encodes an RNA polymerase that is operable during step (d).

1           **67.**     The method according to claim **61**, wherein the non-native promoter is  
2           a phage promoter.

1           **68.**     The method according to claim **62**, wherein said inhibiting is caused by  
2           administering an inhibitor to said biological compartment in an amount sufficient to cause  
3           said inhibiting.

1           **69.**     The method according to claim **68**, wherein said inhibitor is rifampicin.

1           **70.**     The method of claim **45**, wherein said selected macromolecule  
2           experiences a local viscosity at least 2 fold greater than the viscosity of pure water, wherein  
3           said local viscosity and said viscosity of said pure water are determined at the same  
4           temperature.

1           **71.**     The method of claim **45**, wherein said selected macromolecule is  
2           present in said biological compartment at a weight percent of up to 0.3% compared to the  
3           total weight of said biological compartment.





1           **87.**     The method of claim **85**, wherein said e cell is a mammalian cell.

1           **88.**     The method of claim **87**, wherein said cell is a human cell.

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